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Reactions of quinoxaline with 3-methyl-1-phenylpyrazol-5-one

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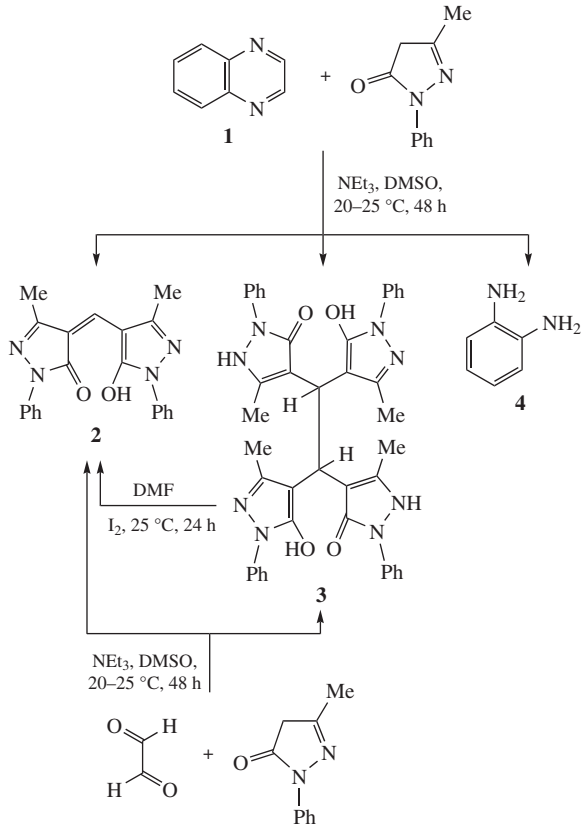
Quinoxaline during the reaction with 3-methyl-1-phenylpyrazol-5-one in the presence of triethylamine at room temperature in dimethylsulfoxide eliminates *o*-phenylenediamine and gives 4,4′-methylene-bis(3-methyl-1-phenylpyrazol-5-one) and 1,1,2,2-tetrakis(5-methyl-2-oxo-2-phenyl-1,2-dihydro-3*H*-pyrazol-4-yl)ethane. The latter was proved to be the intermediate to form the above dipyrazolylmethane derivative.

N-Alkylquinoxalinium salts react with 1,3-diketones to afford products of diaddition or cycloaddition at the C^2–C^3 bond.[1,2] Herein, we report that unsubstituted quinoxaline **1** reacts with 3-methyl-1-phenylpyrazol-5-one in DMSO in the presence of triethylamine at room temperature to give a known dipyrazolylmethane **2**[3] and 1,1,2,2-tetrakis(5-methyl-2-oxo-2-phenyl-1,2-dihydro-3*H*-pyrazol-4-yl)ethane **3**. Besides these compounds, *o*-phenylenediamine **4** was isolated from the reaction mixture by preparative TLC (Scheme 1).†

Products **2** and **3** were also obtained upon refluxing compound **1** with 3-methyl-1-phenylpyrazol-5-one in butanol in the absence of bases.

Tetrapyrazolylethane **3** has a characteristic two-proton singlet signal of the equivalent ethane protons at δ 4.74.† The high-resolution mass spectrum (HRMS, ESI-MS)‡ of compound **3** shows two-charge and one-charge molecular ions: 360.1573 (calc. for $C_{42}H_{40}N_8O_4$, $[M+2H]^{2+}$ 360.1581, $\Delta m/m$ = 2.2 ppm) and 719.3075 (calc. for $C_{42}H_{39}N_8O_4$, $[M+H]^+$ 719.3089, $\Delta m/m$ = 2 ppm).



Scheme 1

Crystallisation from aqueous DMF gave crystals of product **3** suitable for X-ray study (Figure 1).§,5

Compound **3** crystallises in centrosymmetrical space group $P2_1/n$, monoclinic system, as a solvate with a DMF molecule.

† *Reaction of quinoxaline* **1** *with 3-methyl-1-phenylpyrazol-5-one*.

A. A mixture of quinoxaline **1** (0.130 g, 1.0 mmol) and 3-methyl-1-phenylpyrazol-5-one (0.522 g, 3.0 mmol) was kept in DMSO (2 ml) in the presence of triethylamine (0.3 ml) for 48 h at room temperature. The reaction mixture was diluted with water (1:1) and acidified with 15% hydrochloric acid to pH 5–6. The precipitate formed was filtered off and washed with hot ethanol (10 ml) to give 0.340 g (47%) of product **3**, mp > 250 °C. The ethanol after washing was cooled and the precipitate was filtered off to give 0.025 g (7%) of compound **2**, which is identical in mp and spectral characteristics (^{1}H NMR, mass spectrum) to dipyrazolylmethane reported in ref. 3. The mother liquor of the reaction mixture was neutralised to pH 7–8 and extracted with chloroform. Then, chloroform was removed *in vacuo*. The resulting precipitate was subjected to preparative TLC on silica gel to yield 0.025 g (23%) of *o*-phenylenediamine **4** (R_f = 0.33, eluent: $CHCl_3$–EtOH, 9:1).

B. A mixture of compound **1** (0.065 g, 0.5 mmol) and 3-methyl-1-phenylpyrazol-5-one (0.174 g, 1.0 mmol) was refluxed in butanol (3 ml) for 4 h. The reaction mixture was cooled; the precipitate formed was filtered off and washed with hot ethanol (10 ml). Then, it was recrystallized with water from DMF at room temperature to afford 0.030 g (8%) of product **3**. The ethanol after washing was cooled and the precipitate was filtered off to provide 0.007 g (4%) of compound **2**.

Reaction of glyoxal with 3-methyl-1-phenylpyrazol-5-one. A mixture of glyoxal sodium bisulfite ($C_2H_2O_2 \times 2NaHSO_3 \times H_2O$) (0.080 g, 0.4 mmol), 3-methyl-1-phenylpyrazol-5-one (0.204 g, 1.2 mmol) and triethylamine (0.1 ml) was kept in DMSO (2 ml) for 48 h at room temperature. The reaction mixture was diluted with water (1:1) and acidified to pH 5–6 with 15% hydrochloric acid. The precipitate formed was filtered off and washed with hot ethanol (5 ml) to give 0.040 g (14%) of compound **3**. The ethanol after washing was cooled and the precipitate was filtered off to give 0.008 g (6%) of compound **2**.

Conversion of tetrakis-pyrazolylethane **3** *to dipyrazolylmethane* **2**.

A. Compound **3** (0.020 g, 0.03 mmol) was heated for 5 min in boiling DMF (2 ml). The reaction mixture was cooled to room temperature and diluted with water (1:1). The precipitate was filtered off to give 0.012 g (60%) of compound **2**.

B. Compound **3** (0.020 g, 0.03 mmol) was dissolved in DMF (1.5 ml) at room temperature, then iodine (0.020 g, 0.08 mmol) was added. The reaction mixture was kept for 24 h at room temperature, then water (0.1 ml) was added to the reaction mixture. The precipitate was filtered off to yield 0.010 g (50%) of compound **2**.

For **3**: ^{1}H NMR (400 MHz, DMSO-d_6 + CF_3COOH) δ: 2.25 (s, 12H, 4Me), 4.74 (s, 2H, CH_{aliph}), 7.25–7.32 (m, 4H, CH_{arom}), 7.42–7.50 (m, 8H, CH_{arom}), 7.60–7.68 (m, 8H, CH_{arom}).

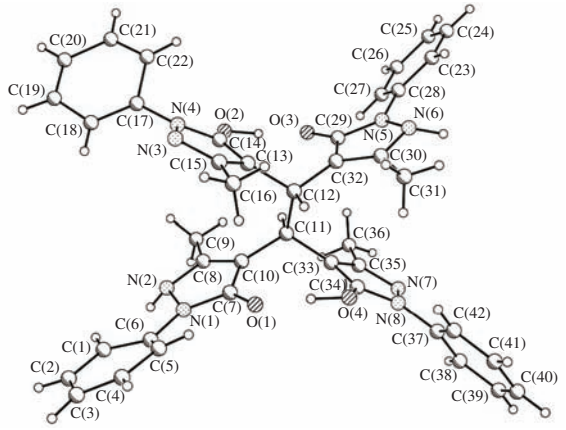


Figure 1 Molecular structure of compound **3**.

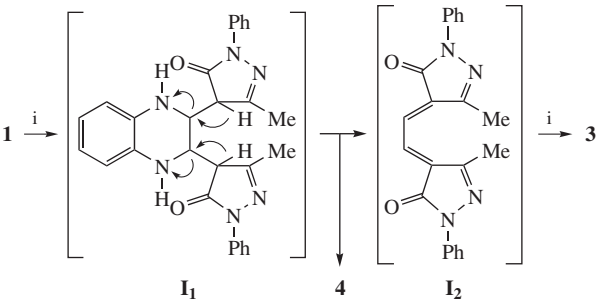
The ethane moiety has standard C–C bond lengths and bond angles. The torsion angles H(11)–C(11)–C(12)–H(12), C(10)–C(11)–C(12)–C(13) and C(33)–C(11)–C(12)–C(32) are in the range of –172±1°. The molecules have an antiperiplanar (*trans* type) conformation. The azolyl substituents are pairwise located in two tautomeric forms, namely, hydroxypyrazole and pyrazolinone forms, which manifests itself in the different geometry of these rings. In fact, the C–C bond lengths in the hydroxypyrazolyl moiety are ~1.40 and 1.37 Å, which differ considerably from those in the non-equivalent pyrazolinone (~1.36 and 1.43 Å, respectively). The C–O bond lengths in the pyrazolyl moieties also differ considerably: ~1.33 Å in the hydroxy form and ~1.26 Å in the keto form. The spatial orientation of the azolyl moieties in the molecule is determined by the existence of intramolecular hydrogen bonds between the carbonyl and hydroxy groups of these rings; the parameters of these bonds are presented in Table 1.

Molecules in a crystal have a layered packing; the layers are arranged in parallel with plane (001). This packing results from the existence of intramolecular hydrogen bonds between the NH groups of the azolyl moieties and between the DMF molecule and the hydroxypyrazole ring.

Table 1 Geometrical parameters of hydrogen bonds in the crystal structure of compound **3**.[a]

D–H···A bond	Distance, Å			D–H···A angle/deg
	D–H	H···A	D···A	
O(2)–H(1AA)–O(3)	1.01(2)	1.49(2)	2.493(2)	174(2)
O(4)–H(2AA)–O(1)	1.02(2)	1.50(2)	2.519(2)	176(2)
N(2)–H(2B)–N(3) 1	0.96(2)	1.89(2)	2.827(2)	168(2)
N(6)–H(6A)–O(5) 2	0.98(2)	1.76(2)	2.717(2)	165(2)

[a] Symmetrical transformations of atoms: 1 (–*x*+3/2, *y*+1/2, –*z*+1/2); 2 (–*x*+1/2, *y*–1/2, –*z*+1/2).



Scheme 2 *Reagents*: i, 2 equiv. of 3-methyl-1-phenylpyrazol-5-one.

We also obtained tetrapyrazolyl derivative **3** by an independent synthesis, *viz.*, the reaction of 3-methyl-1-phenylpyrazol-5-one with glyoxal in DMSO in the presence of triethylamine. The mechanism of tetrapyrazolylethane **3** formation apparently involves the following steps: (*a*) nucleophilic addition of two 3-methyl-1-phenylpyrazol-5-one molecules to the C=N bonds of quinoxaline **1** to form bis-adduct $\mathbf{I_1}$ (Scheme 2) and (*b*) cleavage of bis-adduct $\mathbf{I_1}$ to give intermediate $\mathbf{I_2}$ followed by conversion of the latter to tetrapyrazolylethane **3**.

It is interesting that even short-term heating of product **3** in DMF at 150 °C results in dipyrazolylmethane **2**. The same conversion in the presence of iodine occurs even at room temperature.

Note that the formation of compound **2** was observed previously[4] in the reaction of quinazoline with 3-methyl-1-phenylpyrazol-5-one and resulted from the cleavage of two C=N heterocycle bonds. However, the formation of compound **2** in reactions of quinoxaline is due to the cleavage of C=N and C=C bonds.

In summary, quinoxaline acts the synthetic equivalent of glyoxal serving as the donor of a one-carbon moiety in the reaction of quinoxaline with 3-methyl-1-phenylpyrazol-5-one to furnish dipyrazolylmethane **2**. It should be, however, noted that cleavage of the C=C bond of the pyrazine ring of quinoxaline results from the homolytic cleavage of tetrapyrazolyl derivative **3**, which is formed initially, at the C–C bond of its ethane moiety.

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‡ The mass spectra were measured on a Bruker Daltonics MicrOTOF-Q II mass spectrometer (Bremen, Germany) with an electrospray ionization source, a 6-port divert valve and syringe pump kd Scientific with flow rate 180 $dm^3\ h^{-1}$. The instrument controls were performed with HyStar 3.2 and micrOTOFcontrol 2.3 patch 1 (Bruker Daltonics) software. The nominal resolution of the instrument was 17500. The instrument was operated in positive ion mode with an *m*/*z* range of 50–800. A 6-point external instrument mass scale calibration was performed before each sequence with lithium formate clusters by infusing 10 mM lithium hydroxide in isopropanol/0.2% formic acid (1:1, v/v).

§ *Crystal data for compound* **3**. The X-ray diffraction study was performed with an Xcalibur 3 single crystal X-ray diffractometer with a CCD detector using the standard procedure [MoKα radiation, $T = 295(2)$ K, ω-scanning, scanning step 1°]. The crystals dimensions were 0.25×0.20×0.15 mm, monoclinic, space group $P2_1/n$, unit cell parameters: $a = 16.6054(10)$, $b = 10.9650(6)$ and $c = 23.7972(17)$ Å, $\beta = 103.142(6)°$, $V = 4219.5(5)$ Å^3, $Z = 4$, $d_{calc} = 1.247$ g cm^{-3}. The number of reflections collected in the range of $2.67° < \theta < 28.29°$ was 26429, 10353 of these were independent ($R_{int} = 0.0365$) and 3945 had $I > 2\sigma(I)$. The experiment completeness at angles within $\theta \leq 26.0°$ was 99.3%. The structure was solved by the direct method and refined by full-matrix least squares method with respect to F^2 using SHELXTL-97 software in anisotropic approximation for non-hydrogen atoms. No correction for absorption was introduced ($\mu = 0.084$ mm^{-1}). The final values of the refined parameters were $R_1 = 0.0413$, $wR_2 = 0.0813$ based on the reflections with $I > 2\sigma(I)$; $R_1 = 0.1236$, $wR_2 = 0.0867$ based on all reflections; *Q*-factor $S = 1.007$. The NH and OH protons were localised on the basis of spatial electron density peaks and refined independently. The positions of the other hydrogen atoms were calculated geometrically and included in the refinement based on a riding model.

CCDC 858777 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.